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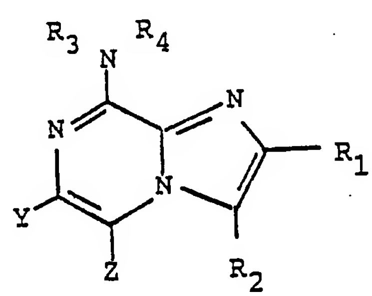
(54) Title: 8-ALKYLAMINOIMIDAZO[1,2-A]PYRAZINES AND DERIVATIVES, THEIR PREPARATION AND THEIR APPLICATION IN THERAPY



(I)

(57) Abstract

Novel 8-alkylamino-imidazo(1,2-a)pyrazines of formula (I) show advantageous pharmacological activities. They can be used for medical products in human and veterinary therapy in the field of applications of antispasmodics, uterine relaxants, bronchodilators, cardiac analeptics and neurosedatives.

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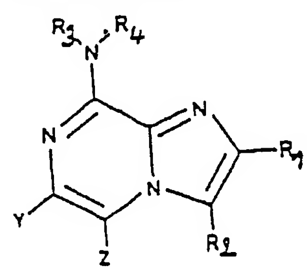
8-Alkylaminoimidazo[1,2-a]pyrazines and derivatives, their preparation and their application in therapy

The present invention relates to 8-alkylamino-imidazo[1,2-a]pyrazines and their derivatives, their preparation and their therapeutic application in human or veterinary medicine in the field of antispasmodics, uterine relaxants, bronchodilators, cardiac analeptics and neuro-sedatives.

Imidazo[1,2-a]pyrazines possessing advantageous pharmacological activities have already been described in the literature, for example in U.S. patents Nos. 4,507,294, 4,483,858, 4,376,772 and 4,242,344, in British patent No. 2,132,203, in European patents Nos. 0,013,914, 0,113,236 and 0,154,494 and in various publications such as those produced by ABIGNENTE, E. et al. Eur. J. Med. Chemistry, 1985, p. 79-85, 20 and SABLAYROLLES C. et al. J. Med. Chem., 1984 p. 206-212, 27.

The present invention encompasses the compounds corresponding to the formula:



as well as the corresponding salts which are compatible with pharmaceutical application.

In this formula (I):

. Y and Z independently denote:

a) a hydrogen atom,

b) a halogen atom such as F, Cl, Br or I,

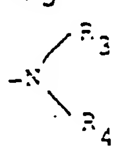
c) CO_2H,

d) CN,

e) a linear or branched C_1-C_5 alkyl radical,

f) a C_1-C_5 alkoxy radical,

g) CF_3

h) 

with R_3 and R_4 as defined below;

. R_1 and R_2, when they are independent, denote,

a) a hydrogen atom,

b) a halogen atom such as F, Cl, Br or I,

c) a linear or branched C_1-C_5 alkyl radical,

d) a radical $-(CH_2)_n-CO_2R_5$, with R_5 denoting a C_1-C_5 alkyl radical and n being between 0 and 4,

e) a phenyl radical, optionally substituted,

f) $CO-N\begin{matrix} \diagup R_6 \\ \diagdown R_7 \end{matrix}$

with R_6 and R_7 independently denoting a hydrogen atom, a linear or branched C_1-C_5 alkyl radical or an aryl radical,

g) CN,

h) $CH_2-N\begin{matrix} \diagup R_6 \\ \diagdown R_7 \end{matrix}$,

i) NH_2,

j) CH_2Cl,

k) CH_2OH,

l) CF_3,

m) $SO_2-N\begin{matrix} \diagup R_6 \\ \diagdown R_7 \end{matrix}$,

n) $-NO_2$,

o) $-NO$,

p) a C_3-C_6 cycloalkyl radical,

q) an acyl radical,

r) a linear or branched C_1-C_5 alkylthio radical;

. R_1 and R_2, when they are linked to one another, denote $-CH_2-CH_2-CH_2-CH_2-$,

. R_3 and R_4 independently denote:

a) a hydrogen atom

b) a linear or branched C_1-C_5 alkyl radical, capable of bearing one or more hydrogen atoms or a hydroxy, $N(C_1$-C_4 alkyl$)_2$, carbamoyl or C_1-C_4 alkoxy radical, either a C_3-C_6 cycloalkyl radical or a phenyl radical,

c) a C_1-C_5 acyl radical,

d) a furfuryl radical,

. R_3 and R_4, linked to one another denote $-CH_2-CH_2-CH_2-CH_2-CH_2$ or $-CH_2-CH_2-X-CH_2-CH_2-$ in which X denotes O or S.

The preferred compounds of the invention are those in which R_3 is a hydrogen atom, R_4 a hydrogen atom or a methyl or ethyl radical, R_1 a hydrogen atom or an ethyl carboxylate group, Y and Z denote either a hydrogen atom or a bromine atom and R_2 denotes either a bromine atom or a hydrogen atom. Among these compounds, there may be mentioned more especially the compound in which R_3=H, R_4=CH_3, Y=H, Z=H, R_2=Br and R_1=H, the compound in which R_3=H, R_4=CH_3, Y=Br, Z=H, R_2=H, R_1=H and the compound in which R_3=H, R_4=H, Y=Br, Z=H, R_2=Br and R_1=H.

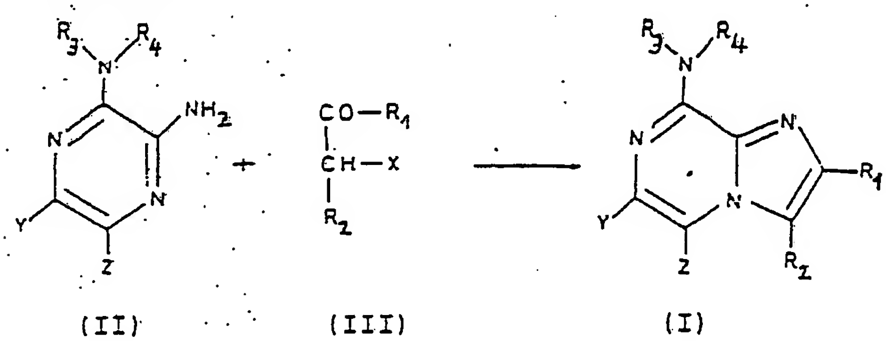
The salts that are compatible with pharmaceutical application are the salts resulting from the neutralization of the basic compounds corresponding to the formula (I) with an acid. The acids employed are either inorganic or organic acids. As examples of such inorganic acids, halogen hydracids, such as hydrochloric acid, hydrobromic acid and hydriodic acid, phosphoric acid, sulfuric acid, and the like should be mentioned. As examples of organic acids, carboxylic acids such as acetic acid, maleic acid, succinic acid, citric acid, tartaric acid, oxalic acid, malic acid, pivalic acid, heptanoic acid, lauric acid, salicylic acid, benzoic acid, glutamic acid, lactic acid, and the like and non-carboxylic acids such as isethionic acid and methanesulfonic acid, should be mentioned. The salts of halogen hydracids, especially the hydrochlorides, the salts of maleic acid, especially the acid maleates, and the salts of methanesulfonic acid are preferred.

According to the invention, the compounds (I) may be prepared according to the reaction schemes 1 and 2 below, which employ known processes and which use known starting substances. The particular methods and the reaction sequences are derived from the specific nature of the substituents and their position.

One of the processes for producing the compounds

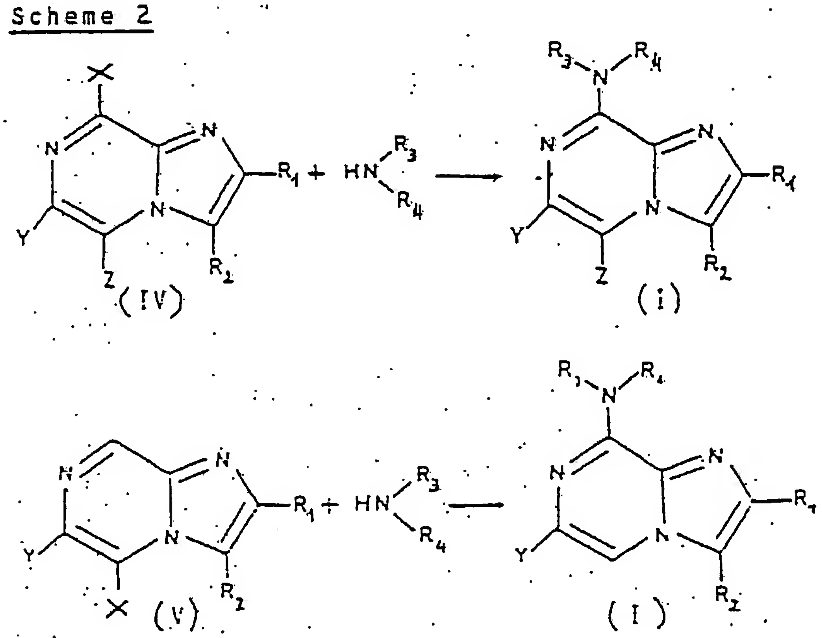
(I) (scheme 1) consists in condensing a 2,3-diamino- or 3-alkylamino-2-aminopyrazine (II) containing the substituents Y and Z with an alpha-halocarbonyl compound (III).

Scheme 1



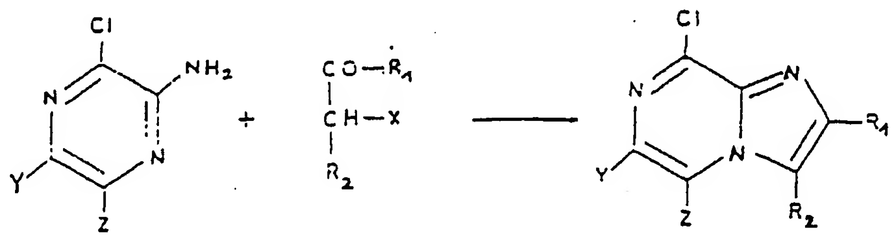
Another process (scheme 2) for producing the compounds (I) consists in carrying out a substitution reaction starting with an imidazo[1,2-a]pyrazine derivative, according to a traditional method, for example by the action of ammonia, alkylamines or a nitrogenous heterocycle on a halogenated derivative. The halogenated derivative used can be either a derivative halogenated at the 8-position (compound IV), or a derivative halogenated at the 5-position (compound V), the substitution reaction in this case being accompanied by a change in the position of substitution (telesubstitution). In the compounds of the formulae (IV) and (V), X denotes a chlorine or bromine atom.

Scheme 2



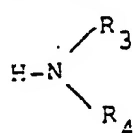
The halogenated derivatives (IV) possessing a halogen at the 8-position may in turn be obtained (scheme 3) from a substituted 2-amino-3-halopyrazine (VI) which is condensed with an alpha-halocarbonyl derivative (III).

Scheme 3

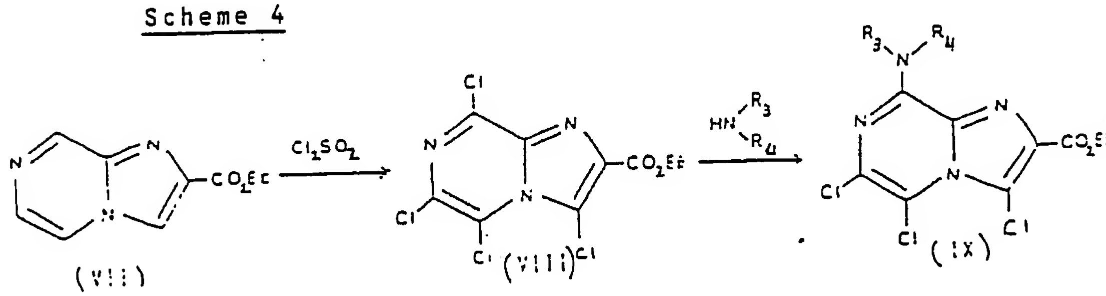


(VI) (III) (IV)

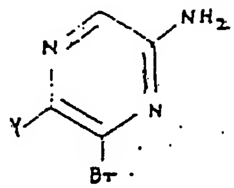
Another method for obtaining a compound of general formula (IV) possessing a chlorine atom at the 8-position consists in treating an imidazo[1,2-a]pyrazine with sulfuryl chloride. There is thus obtained, for example, from ethyl imidazo[1,2-a]pyrazine-2-carboxylate (VII), a mixture of ethyl trichloro- and 5,6,7,8 tetrachloroimidazo-[1,2-a]pyrazine-2-carboxylate (VIII) (scheme 4), in which the chlorine at the 8-position is the atom which may be most readily substituted by an amine of type:



Scheme 4



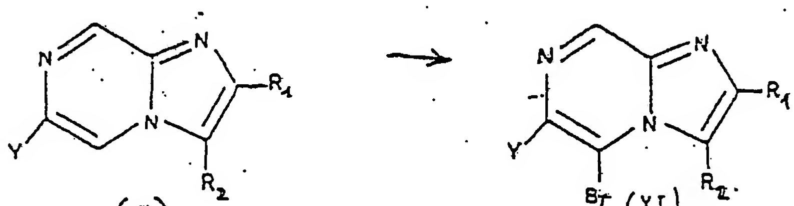
The halogenated derivatives possessing a halogen atom at the 5-position (compound V) may be obtained according to the above process (scheme 3), replacing the compound (VI) by the compound (VI')



(VI')

in which the halogen is, for example, a bromine atom, but also by direct halogenation (scheme 5) of a substituted imidazo[1,2-a]pyrazine possessing a hydrogen atom at the 5-position, using the usual reagents, for example bromine in ethanol or acetic acid, N-bromosuccinimide, and the like.

Scheme 5



The 2-amino pyrazines (VI) and (VI'), the alpha-halocarbonyl compounds (III) and the imidazo[1,2-a]pyrazines (VII) and (X) employed in the production methods described above are commercial products or products prepared from common starting substances by traditional methods known to those versed in the art.

The groups R_1, R_2, Y and Z of the general formula (I) of the compounds of the invention are provided by the starting compounds (VI), (VI'), (II) and (III) or are obtained after condensation to the corresponding substituted imidazo[1,2-a]pyrazine. For example, nucleophilic substitution reactions are carried out starting out with derivatives halogenated at the 3-, 5- and 6-positions, using traditional nucleophilic reagents (CN^-, X^-, HNR_3R_4, RO^-, RS^-, and the like); an ester group is converted to amide by the action of ammonia in concentrated aqueous solution, and then either to an amine by the action of sodium hypobromite or to a nitrile by dehydration using

phosphorus oxytribromide. A chloromethyl group leads via the action of ammonia to an aminomethyl group, or via the action of an N-alkylamine to an N-alkylaminomethyl group.

In the same manner, different derivatives may be prepared from an imidazo[1,2-a]pyrazine by an electrophilic substitution reaction on the unsubstituted 3-position. A trifluoroalkylthio group is thereby obtained via the action of trifluoromethanesulfonylchloride and the sulfonamide derivative via the action of chlorosulfonic acid followed by thionyl chloride and an amine, such as methylamine, for example. Similarly, reaction of N-bromosuccinimide or N-chlorosuccinimide yields, respectively, the derivatives brominated or chlorinated at the 3-position. Perchloryl fluoride yields the derivative fluorinated at the 3-position. The action of nitrous acid prepared at the time of use or butyl nitrite gives the nitroso derivative. The nitro derivative results from the action of nitric acid in sulfuric medium.

The examples which follow are given by way of illustration and in no way imply limitation of the invention.

The analyses and the IR, NMR and MS spectra confirm the structure of the compounds.

Example 1

3-Bromo-8-methylaminoimidazo[1,2-a]pyrazine.

Stage A: preparation of imidazo[1,2-a]pyrazine

A mixture of 34 g (0.2 mol) of bromoacetaldehyde dimethyl acetal, 6,6 ml of concentrated aqueous HBr solution and 28 ml of distilled water is brought to reflux for one hour. After reaction, the mixture is alkalinized and extracted with ether. This organic phase is added to a solution of 19 g (0.2 mol) of aminopyrazine in 50 ml of dimethylformamide (DMF). The ether is removed by distillation and the mixture is maintained with stirring and under a stream of nitrogen for 12 hours. After reaction, the DMF is distilled off; the reaction medium is dissolved in 150 ml of anhydrous ethanol, and then brought to reflux for one hour. The alcohol is then removed by distillation; the

residue is dissolved in water, alkalinized with Na_2CO_3 and extracted using dichloromethane. After chromatography on a neutral alumina column (eluant = anhydrous ether), 10.7 g (Yld = 45%) of imidazo[1,2-a]pyrazine (m.p. 84°C). are obtained.

Stage B: preparation of 3,5-dibromoimidazo[1,2-a]-pyrazine.

A solution of 12 ml of bromine in 10 ml of acetic acid is added dropwise to a solution of 6 g (50.5 mmol) of imidazo[1,2-a]pyrazine in 70 ml of acetic acid. The solution brought to reflux for one and a half hours is then evaporated under vacuum. The residue is then dissolved in water, alkalinized with Na_2CO_3 and extracted with dichloromethane. After chromatography on a neutral alumina column (eluant = anhydrous ether), 8,38 g (Yld = 60%) of 3,5-dibromoimidazo[1,2-a]pyrazine (m.p. 150°C) are obtained.

Stage C: preparation of 3-bromo-8-methylamino-imidazo[1,2-a]pyrazine.

A mixture of 1 g (3,6 mmol) of 3,5-dibromoimidazo-[1,2-a]pyrazine in 9 ml of a 40% strength aqueous methylamine solution is maintained with stirring for 12 hours. After evaporation under reduced pressure and chromatography on a silica column eluted with ether, 0.33 g (Yld = 40%) of 3-bromo-8-methylaminoimidazo[1,2-a]pyrazine (m.p. 139°C) is obtained.

By replacing, in Example 1 above, stage C, methylamine by:

ammoniacal alcohol, 8-amino-3-bromoimidazo[1,2-a]-pyrazine (m.p. 239°C) is obtained;

ethylamine, 3-bromo-4-ethylaminoimidazo[1,2-a]-pyrazine (m.p. 82°C) is obtained.

Example 2

8-Morpholinoimidazo[1,2-a]pyrazine.

Stage A: preparation of 6,8-dibromoimidazo[1,2-a]-pyrazine.

This derivative is obtained according to a technique identical to that of Example 1, stage A, by replacing 2-aminopyrazine by 2-amino-3,5-dibromopyrazine. 10 g

(39.5 mmol) of this compound yield 5.47 g (Yld = 50%) of 6,8-dibromoimidazo[1,2-a]pyrazine (m.p. 165°C).

Stage B: preparation of 6-bromo-8-morpholino-imidazo[1,2-a]pyrazine.

A solution of 1 g (3,6 mmol) of 6,8-dibromo-imidazo[1,2-a]pyrazine and 1 g (11.2 mmol) of morpholine in 15 ml of anhydrous ethanol is brought to reflux for 12 hours. After evaporation of the solvant and chromatography on an alumina column (eluant = CH_2Cl_2), 0.88 g (Yld = 85%) of 6-bromo 8-morpholinoimidazo[1,2-a]pyrazine (m.p. 191°C) is obtained.

Stage C: preparation of 8-morpholinoimidazo[1,2-a]-pyrazine.

200 mg of palladium on charcoal (10% palladium) are added to a solution containing 0.5 g (1.77 mmol) of 6-bromo-8-morpholinoimidazo[1,2-a]pyrazine for 120 ml of anhydrous methanol and 2 g of potassium hydroxide. The mixture is hydrogenated at atmospheric pressure for 12 hours. The solution is filtered, concentrated and taken up with water; after extraction with dichloromethane and evaporation of the solvent, 0.34 g (92%) of 8-morpholino-imidazo[1,2-a]pyrazine (m.p. 127°C) is obtained.

By replacing, in Example 2 above, stage B, morpholine by the different amines referred to in Table I below, the corresponding substituted 6-bromoimidazo[1,2-a]-pyrazines, recorded in the same table, are obtained. Treatment of the products thereby obtained according to the process described in Example 2, stage C, yields the substituted imidazo[1,2-a]pyrazines referred to in Table I.

Table I

Amines	Results of stage B	Result of Stage C
Ammoniacal alcohol	8-amino-6-bromoimidazo-[1,2-a]pyrazine (m.p. 210°C)	8-aminoimidazo[1,2-a]-pyrazine (m.p. 220°C)
Methylamine	6-bromo-8-methylamino-imidazo[1,2-a]pyrazine (m.p. 162°C)	8-methylaminoimidazo-[1,2-a]pyrazine (m.p. 96°C)
Ethylamine	6-bromo-8-ethylamino-imidazo[1,2-a]pyrazine (m.p. 99°C)	8-ethylaminoimidazo-[1,2-a]pyrazine (m.p. 98°C)
Furfuryl-amine	6-bromo-8-furfurlamino-imidazo[1,2-a]pyrazine (m.p. 164°C)	8-furfurylaminoimidazo-[1,2-a]pyrazine (m.p. = pasty)

Example 3

Ethyl 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-acetate.

Stage A: preparation of 2-amino-5-bromo-3-methyl-aminopyrazine.

1.55 g (50 mmol) of 40% strength aqueous methylamine solution is added to a solution of 2.53 g (10 mmol) of 3,5-dibromo-2-aminopyrazine in ethanol. The mixture is stirred in an autoclave at 130°C for 17 hours. After evaporation of the solvent under reduced pressure, the product is purified by chromatography on a silica column (eluant = CH_2Cl_2, to which 3% of CH_3OH has been added). 0.8 g (Yld = 40%) of 2-amino-5-bromo-3-methylaminopyrazine (m.p. 121°C) is obtained.

Stage B: preparation of ethyl 6-bromo-8-methylamino-imidazo[1,2-a]pyrazine-2-acetate.

2.03 g (10 mmol) of 2-amino-5-bromo-3-methylamino-pyrazine are dissolved in 5 ml of dimethylformamide (DMF). A solution of 1.645 g (10 mmol) of ethyl (chloroacetyl)acetate in 5 ml of DMF is added dropwise with stirring. The mixture is maintained with stirring and under gentle reflux for 3 hours. The DMF is then evaporated off under reduced pressure and the residue, dissolved in 50 ml of anhydrous ethanol, is brought to reflux for one hour. After removal of the

solvent, the residue is taken up with water, alkalinized and extracted with dichloromethane. After dehydration over anhydrous calcium chloride, the solvent is evaporated off under reduced pressure. The crude product is purified by chromatography on a silica column (eluant = dichloromethane to which 5% of methanol has been added). 0.4 g (Yld = 30%) of ethyl 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-acetate (m.p. 104°C) is obtained.

By replacing, in the Example 3 above, stage B, 2-amino-5-bromo-3-methylaminopyrazine by an equimolar amount of substituted 2-aminopyrazines and ethyl (chloroacetyl)acetate by ethyl bromopyruvate, the 8-aminoimidazo[1,2-a]pyrazine derivatives appearing in Table II below are obtained.

For the final derivative listed in this Table II, only the replacement of 2-amino-5-bromo-3-methylaminopyrazine by the substituted 2-aminopyrazine is necessary.

Table II

Substituted 2-aminopyrazines:	8-Aminoimidazo[1,2-a]pyrazine derivatives:
2,3-diaminopyrazine	ethyl 8-aminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 230°C).
2,3-diamino-5-bromopyrazine	ethyl 8-amino-6-bromoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 245°C).
2-amino-3-methylaminopyrazine	ethyl 8-methylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 184°C).
2-amino-5-bromo-3-methylaminopyrazine	ethyl 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 234°C).
2-amino-5-bromo-3-ethylaminopyrazine	ethyl 6-bromo-8-ethylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 180°C).
2-amino-3-propylaminopyrazine	ethyl 8-propylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 145°C).
2-amino-5-bromo-3-propylaminopyrazine	ethyl 6-bromo-8-propylaminoimidazo[1,2-a]pyrazine-2-

	carboxylate (m.p. 190°C).
2-amino-5-bromo-3-butylaminopyrazine	ethyl 6-bromo-8-butylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 176°C).
2-amino-5-bromo-3-sec-butylaminopyrazine	ethyl 6-bromo-8-sec-butylaminoimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 187°C).
2-amino-3-piperidylpyrazine	ethyl 8-piperidylimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 114°C).
2-amino-5-bromo-3-piperidylpyrazine	ethyl 6-bromo-8-piperidylimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 134°C).
2-amino-3-morpholinylpyrazine	ethyl 8-morpholinylimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 155°C).
2-amino-5-bromo-3-morpholinylpyrazine	ethyl 6-bromo-8-morpholinylimidazo[1,2-a]pyrazine-2-carboxylate (m.p. 140°C).
2-amino-5-bromo-3-(2-hydroxyethylamino)pyrazine	ethyl 6-bromo-8-(2-hydroxyethylamino)imidazo[1,2-a]pyrazine-2-carboxylate (m.p. 208°C).
2,3-diamino-5-bromopyrazine	ethyl 8-amino-6-bromoimidazo[1,2-a]pyrazine-2-acetate (m.p. 181°C).

Example 4

5-Chloro-8-ethylaminoimidazo[1,2-a]pyrazine.

Stage A: preparation of 5,8-dichloroimidazo[1,2-a]pyrazine.

This derivative is obtained according to a technique identical to that of Example 1, stage A, by replacing 2-aminopyrazine by 2-amino-3,6-dichloropyrazine. 2.4 grams (18.6 mmol) of this compound yield 1 g (Yld = 37%) of 5,8-dichloroimidazo[1,2-a]pyrazine (m.p. 102°C).

Stage B: preparation of 8-ethylamino-5-chloroimidazo[1,2-a]pyrazine.

A solution of 1.5 g (9.8 mmol) of 5,8-dichloro-

imidazo[1,2-a]pyrazine in 25 ml of a 40% strength aqueous ethylamine solution is maintained with stirring for 12 hours. After concentration under reduced pressure and chromatography on a silica column (eluant = ether), 5-chloro-8-ethylaminoimidazo[1,2-a]pyrazine (m.p. 94°C), is obtained.

Example 5

8-Amino-3,6-dibromoimidazo[1,2-a]pyrazine.

Stage A: preparation of 3,6,8-tribromoimidazo-[1,2-a]pyrazine.

A solution of 0.8 g (2.9 mmol) of 6,8-dibromo-imidazo[1,2-a]pyrazine and 1.2 g of N-bromosuccinimide in 40 ml of chloroform is brought to reflux for two hours. After being cooled, the organic solution is treated with aqueous Na_2CO_3 solution. The chloroform phase is collected and then evaporated. 1 g (Yld = 97%) of 3,6,8-tribromoimidazo[1,2-a]pyrazine (m.p. 161°C) is obtained.

Stage B: preparation of 8-amino-3,6-dibromo-imidazo[1,2-a]pyrazine.

A solution of 1 g (2.8 mmol) of 3,6,8-tribromo-imidazo[1,2-a]pyrazine in 50 ml of ammoniacal alcohol heated to 120°C for 5 hours in a 250-ml autoclave. After reaction and evaporation of the solvent, 0.8 g (Yld = 98%) of 8-amino-3,6-dibromoimidazo[1,2-a]pyrazine (m.p. = 246°C) is obtained.

By replacing, in Example 5 above, stage B, ammoniacal alcohol by:

.methylamine, 3,6-dibromo-8-methylaminoimidazo-[1,2-a]pyrazine (m.p. 229°C) is obtained;

or ethylamine, 3,6-dibromo-8-ethylaminoimidazo-[1,2-a]pyrazine (m.p. 131°C) is obtained;

or morpholine, 3,6-dibromo-8-morpholinoimidazo-[1,2-a]pyrazine (m.p. 141°C) is obtained;

or furfurylamine, 3,6-dibromo-8-furfurylaminoimidazo-[1,2-a]pyrazine (m.p. 143°C) is obtained;

or piperidine, 3,6-dibromo-8-piperidylimidazo-[1,2-a]pyrazine (m.p. 72°C) is obtained.

Example 6

6-Bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-

carboxamide.

A suspension of 0.470 g (1.57 mmol) of ethyl 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-carboxylate, obtained according to the process described in Example 3, in 50 ml of concentrated aqueous ammonia solution, is brought to reflux for 4 hours. After the mixture is cooled, the precipitate is drained, washed and dried. 0.160 g (Yld = 40%) of 6-bromo-8-methylaminoimidazo-[1,2-a]pyrazine-2-carboxamide (m.p. 312°C) is obtained.

Example 7

3,5,6-Trichloro-8-methylamino-N-methylimidazo-[1,2-a]pyrazine-2-carboxamide.

Stage A: preparation of ethyl imidazo[1,2-a]-pyrazine-2-carboxylate.

This derivative is obtained according to the technique described in Example 3, stage B, by reacting 2-aminopyrazine and ethyl bromopyruvate. Ethyl imidazo-[1,2-a]pyrazine-2-carboxylate (m.p. 179°C, Yld = 25%) is obtained.

Stage B: preparation of ethyl 3,5,6,8-tetrachloro-imidazo[1,2-a]pyrazine-2-carboxylate.

4 ml of sulfuryl chloride are added with stirring to a suspension of 0.720 g (3.77 mmol) of ethyl imidazo-[1,2-a]pyrazine-2-carboxylate in 10 ml of anhydrous benzene, and the mixture is then brought to reflux for one hour. The solvent is then evaporated off under reduced pressure. The residue is poured onto ice, and then extracted after alkalinization. A mixture of 0.750 g (70%) of ethyl trichloroimidazo[1,2-a]pyrazine-2-carboxylate, m.p. 132°C, and 0.350 g (30%) of ethyl 3,5, 6,8-tetrachloro-imidazo[1,2-a]pyrazine-2-carboxylate (m.p. 171°C) is thereby obtained, and these are separated by chromatography on a silica column (eluant = dichloromethane to which 2% of methanol has been added).

Stage C: preparation of 8-methylamino-3,5,6-trichloro-N-methylimidazo[1,2-a]pyrazine-2-carboxamide.

0.330 g (0.1 mmol) of ethyl 3,5,6,8-tetrachloro-imidazo[1,2-a]pyrazine-2-carboxylate, obtained according to the above method, is dissolved at room temperature and

with stirring in 20 ml of a concentrated aqueous methylamine solution. After extraction with dichloromethane, 0.296 g (96%) of 8-methylamino-3,5,6-trichloro-N-methylimidazo[1,2-a]pyrazine-2-carboxamide, m.p.262°C. and 0.02 g of ethyl 8-methylamino-3,5,6-trichloroimidazo-[1,2-a]pyrazine-2-carboxylate are isolated.

Example 8

6-Bromo-8-methylaminoimidazo[1,2-a]pyrazin-2-amine.

0.42 g of bromine (8 mmol) is added to a solution, cooled with a mixture of ice and salt, of 1.9 g of NaOH (47.5 mmol) in 10 ml of water. After the addition of 1.62 g (6 mmol) of 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-carboxamide (obtained according to Example 6), the mixture is brought to reflux for half an hour. After the mixture is cooled, the precipitate formed is collected and the mother liquors are evaporated to dryness. These two fractions are treated with 10% strength HCl until the evolution of gas has ceased. The acid solution is then alkalinized. Extraction with dichloromethane gives 6-bromo-8-methylaminoimidazo[1,2-a]pyrazin-2-amine.

Example 9

6-Bromo-8-methylamino-2-phenylimidazo[1,2-a]-pyrazine.

Stage A: preparation of 6,8-dibromo-2-phenylimidazo[1,2-a]pyrazine.

This derivative is obtained according to a technique identical to that of Example 2, stage A, by replacing bromoacetaldehyde dimethyl acetal by 1-bromoacetophenone. 10 g (39.5 mmol) of 3,5-dibromo-2-aminopyrazine yield 8.3 g (Yld = 60%) of 6,8-dibromo-2-phenylimidazo[1,2-a]pyrazine (m.p. 254°C).

Stage B: preparation of 6-bromo-8-methylamino-2-phenylimidazo[1,2-a]pyrazine.

This derivative is obtained according to a technique identical to that of Example 2, stage B, by replacing morpholine by concentrated aqueous methylamine solution. 6-Bromo-8-methylamino-2-phenylimidazo[1,2-a]pyrazine is obtained.

Example 10

6-Bromo-2-chloromethyl-8-dimethylaminoimidazo-[1,2-a]pyrazine.

Stage A: preparation of 2-amino-5-bromo-3-dimethylaminopyrazine.

This derivative is obtained according to a technique identical to that of Example 3, stage A, by replacing methylamine by a 40% aqueous dimethylamine solution. 5 g (19.8 mmol) of 2-amino-3,5-dibromopyrazine give 3.18 g (Yld = 74%) of 2-amino-5-bromo-3-dimethylaminopyrazine (m.p.145°C).

Stage B: preparation of 6-bromo-2-chloromethyl-8-dimethylaminoimidazo[1,2-a]pyrazine.

1.17 g (9.2 mmol) of 1,3-dichloroacetone is added dropwise to a solution of 2 g (9.2 mmol) of 2-amino-5-bromo-3-dimethylaminopyrazine. After 3 hours under reflux, the alcohol is evaporated off under reduced pressure and the residue taken up with water, alkalinized and extracted with dichloromethane. After purification by chromatography, 6-bromo-2-chloromethyl-8-dimethylaminoimidazo[1,2-a]pyrazine is obtained.

Example 11

6-Bromo-8-morpholinoimidazo[1,2-a]pyrazine-2-carbonitrile

Stage A: preparation of 6,8-dibromoimidazo-[1,2-a]pyrazine-2-carboxamide.

This derivative is obtained according to a technique identical to that described in Example 6, by replacing ethyl 6-bromo-8-methylaminoimidazo[1,2-a]pyrazine-2-carboxylate by ethyl 6,8-dibromoimidazo[1,2-a]pyrazine-2-carboxylate.

Starting with 3.5 g (10 mmol) of ester, 2.56 g of amide (Yld = 80%) (m.p. 260°C) are obtained.

Stage B: preparation of 6,8-dibromoimidazo-[1,2-a]pyrazine-2-carbonitrile.

A suspension of 1 g (3.1 mmol) of amide obtained in stage A above in 9 ml of phosphorus oxytribromide is brought to reflux for one hour. After dissolution, the excess $POBr_3$ is driven off by distillation. The residue

is carefully poured onto ice. After alkalinization, extraction yields 0.6 g (63%) of 6,8-dibromoimidazo[1,2,-a]pyrazine-2-carbonitrile (m.p. 208°C).

Stage C: preparation of 6-bromo-8-morpholinoimidazo[1,2-a]pyrazine-2-carbonitrile.

0.2 g (0.66 mmol) of nitrile is dissolved at room temperature and with stirring (one hour) in 3 ml of morpholine. After evaporation of the excess morpholine under reduced pressure, the residue is taken up with dichloromethane. The evaporated filtered solution yields 0.2 g (Yld = 98%) of 6-bromo-8-morpholinoimidazo[1,2-a]-pyrazine-2-carbonitrile (m.p. 265°C).

The compounds which form the subject of the invention, as well as their pharmaceutically usable salts, possess pharmacological properties justifying their application in human or veterinary therapy. In particular, some derivatives proved to be endowed with greater antispasmodic, uterine relaxant, bronchodilatory and cardiac analeptic (inotropic and positive chronotropic function) activities than those of theophylline (Theo), chosen as reference constituent. It will be noted, in addition, that the compounds which form the subject of the present invention do not possess the neurostimulatory side effects of Theo and that, on the contrary, they prove to be endowed with neurosedative properties.

The demonstration of the pharmacological activities of some of the compounds of the present invention was carried out according to the tests described below. The test compounds are identified by a number corresponding to the structures specified in Table III below.

1. <u>Antispasmodic activity</u>

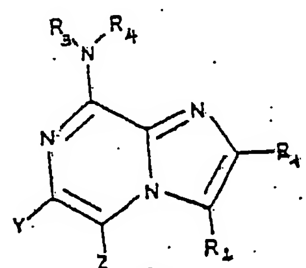
Fragments of duodenum are removed from male rats (200 g), fasted for 24 hours and killed by decapitation, and are mounted, after being washed, in a thermostatted (37°C) isolated organ cell and maintained in survival in Tyrode's solution according to Magnus's classical technique.

The spasmogenic agent used is barium chloride (10^{-4}M).

In the first instance, the spasmogenic agent is added to the nutrient bath and, as soon as the contraction of the organ reaches its maximum, the relaxant agent is added to the medium. Working in relation to a fixed concentration of barium chloride with variable concentrations of relaxant, the ED_{50} of the latter, capable of reducing the induced contraction by 50%, is determined.

The results expressed in Table IV below show the ratio ED_{50} Theo/ED_{50} product, established on the basis of the mean of the results of 5 to 6 determinations per product (ED_{50}theophylline = 8×10^{-4}M).

Table III



(I)

Compound No.	Y	Z	R_1	R_2	R_3	R_4	M.p. (°C)
1	H	H	H	H	H	H	220
2	H	H	H	H	H	CH_3	96
3	H	H	H	H	H	C_2H_5	98
4	H	H	H	H	$-(CH_2)_2-O-(CH_2)_2-$		127
5	H	H	H	Br	H	H	239
6	H	H	H	Br	H	CH_3	143
7	H	H	H	Br	H	C_2H_5	82
8	Br	H	H	H	H	H	210
9	Br	H	H	H	H	CH_3	162
10	Br	H	H	H	H	C_2H_5	99
11	Br	H	H	H	$-(CH_2)_2-O-(CH_2)_2-$		191
12	H	Cl	H	H	H	C_2H_5	94
13	Br	H	H	Br	H	H	246
14	Br	H	H	Br	H	CH_3	229
15	Br	H	H	Br	H	C_2H_5	131
16	Br	H	H	Br	$-(CH_2)_2-O-(CH_2)_2-$		151
17	H	H	CO_2Et	H	H	H	230
18	H	H	CO_2Et	H	H	CH_3	184
19	H	H	CO_2Et	H	H	C_3H_7	145
20	H	H	CO_2Et	H	$-(CH_2)_5-$		114
21	H	H	CO_2Et	H	$-(CH_2)_2-O-(CH_2)_2-$		155
22	Br	H	CO_2Et	H	H	H	245
23	Br	H	CO_2Et	H	H	CH_3	234
24	Br	H	CO_2Et	H	H	C_2H_5	180
25	Br	H	CO_2Et	H	H	C_3H_7	190
26	Br	H	CO_2Et	H	H	$n-C_4H_9$	176
27	Br	H	CO_2Et	H	H	$s-C_4H_9$	187
28	Br	H	CO_2Et	H	$-(CH_2)_5-$		134
29	Br	H	CO_2Et	H	$-(CH_2)_2-O-(CH_2)_2-$		140
30	Br	H	CO_2Et	H	H	$-(CH_2)_2OH$	208
31	Br	H	$CONH_2$	H	H	CH_3	312
32	Br	H	CH_2CO_2Et	H	H	H	181
33	Br	H	CH_2CO_2Et	H	H	CH_3	104

Table III (continued)

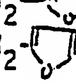
34	Cl	Cl	$CONHCH_3$	Cl	H	CH_3	262
35	Br	H	C≡N	H	$-(CH_2)_2-O-(CH_2)_2-$		265
36	Br	H	H	H	H	$-CH_2-$	164
37	Br	H	H	Br	H	$-CH_2-$	143
38	Br	H	H	Br	$-(CH_2)_5-$		72
39	H	H	H	H	H	$-CH_2-$	pasty

Table IV - Antispasmodic activity

Product	ED_{50} Theo/ED_{50} product
6	32
8	32
9	20
10	40
12	27
17	13

2. Uterine relaxant activity

Female rats (150 - 180 g) are killed by decapitation 24 hours after the intraperitoneal administration of stilbestrol (0.1 mg/kg). The uterine horns are removed and fragments mounted in a thermostatted (37°C) isolated organ cell and maintained in survival in oxygenated De Jalon's solution of composition (mM): NaCl (153.8); KCl (5.6); $CaCl_2$ (2.16); $NaHCO_3$ (1.8); dextrose (5.5). One end of the uterine fragment is maintained fixed, while the other is attached to a recording myograph under a tension of the order of 0.5 g. The spontaneous uterine contractions are recorded on a kymograph. The organ is left at rest for 30 minutes and washed three times. The test products are introduced directly into the bath after being dissolved in De Jalon's solution, and the activity measured (ED_{50}) corresponds to the dose capable of reducing the magnitude of the spontaneous contractions by 50%.

The results expressed in Table V below show the ratio ED_{50} Theo/ED_{50} product, established on the basis of

the mean of the results of 5 to 10 determinations per product. (ED_{50} theophylline = 0.9×10^{-3} M).

Table V - Uterine relaxant activity

Compound	ED_{50} Theo/ED_{50} product
6	9
8	3
9	5.6
10	7.2
17	2.6

3. Antibronchospastic activity

3.1. Bronchospasm induced in guinea pigs

Guinea pigs of both sexes weighing between 400 and 600 g are anesthetized with ethyl carbamate (1.20/kg i.p.). After tracheotomy, the animal is placed under artificial respiration at a constant flowrate (Palmer pump 1 ml/100 g x 60/min). A take-off at the tracheal cannula enables the volume of air to be gaged at each inhalation by means of a Marey drum. Bronchospasm is induced by intraveneous (jugular) administration of histamine. For each animal, the dose of histamine (8 to 12 µg/kg) inducing an increase in the recording trace equal to double its initial value is determined. The dose adopted should provide three identical responses at intervals of 10 minutes.

The test product is administered intraveneously and then, 30 seconds later, histamine is administered again. The measured ED_{50} represents the dose which reduces the histamine-induced bronchoconstriction by 50%. Table VI below shows the ratio ED_{50} Theo/ED_{50} product, established on the basis of the mean of the results of 5 to 8 determinations per product (ED_{50} Theo = 4.3×10^{-5} M/kg).

Product	ED_{50} Theo/ED_{50} product	Product	ED_{50} Theo/ED_{50} product
5	2	23	1
6	2	24	1
8	4	25	< 1
9	5.4	26	< 1
10	2	27	< 1
11	1	28	< 1
13	3.5	29	1
14	1.9	30	< 1
15	1.6	31	1
16	1	32	1.6
17	1.1	33	1
18	1	34	1.2
19	< 1	35	< 1
20	1	36	< 1
21	< 1	37	1.4
22	1.5	38	1.1

3.2. Isolated guinea pig trachea

Guinea pigs of both sexes weighing on average 400 to 600 g are sacrificed, and the tracheas are removed and placed at 37°C in an oxygenated environment (95% O_2 - 5% CO_2) in Krebs fluid of the following composition (mM): NaCl (116), $MgSO_4$ (1.2), KCl (3.7), $CaCl_2$ (2.6), KH_2PO_4 (2.2), $NaHCO_3$ (24.9), glucose (10). The tracheal segments are then mounted horizontally between two hooks, one of which is fixed to the base of the isolated organ cell and the other is attached to a myograph under a tension of 0.5 g. The organ is left at rest for one hour and is subjected to four washes. The contraction-inducing reagent (carbachol) is added at a concentration (10^{-4}M) greater than the concentration giving the maximum effect. After stabilization of the contractional effect, gradually increasing accumulative amounts of the test products are added to the cell. The bronchodilatory effect is measured as the percentage inhibition of the maximal contraction and

EC_{50} represents the concentration inhibiting this concentration by 50%.

Table VII below shows the ratio EC_{50} theophylline/EC_{50} product, established on the basis of the mean of the results of 5 to 6 determinations by product (EC_{50} Theo $= 10^{-3}$M).

Table VII - Anti-contractional activity (trachea)

Product	EC_{50} Theo/EC_{50} product	Product	EC_{50} Theo/EC_{50} product
1	1.5	7	5
2	<1	8	11.3
3	1	9	8.3
4	<1	10	5
5	11	11	<1
6	12.5	39	<1

4. Cardiac activity (inotropic and chronotropic function)

Guinea pigs of both sexes weighing between 300 and 500 g are killed by decapitation. The hearts are rapidly removed and placed in an oxygenated environment (95% O_2 - 5% CO_2) in Chenoweth-Koelle's solution of the following composition (mM): NaCl (120), KCl (5.63), $CaCl_2$ (2.0), dextrose (9.7), $MgCl_2$ (2.0), $NaHCO_3$ (26.0). The right and left atria are then separated from the heart and mounted in an isolated organ cell. The right atrium beats spontaneously and the left atrium is electrically stimulated. The organs under a tension of 1 g are left at rest for two hours and washed every fifteen minutes.

The products are added directly to the nutrient bath. The right atrium is used for measuring the modifications of rate (chronotropic function) whereas the left atrium indicates the modifications brought about in the contractile force (inotropic function).

For the inotropic function, the concentration capable of producing an increase in magnitude of 0.5 g with respect to the basic contraction is measured.

For the chronotropic function, the concentration capable of producing a 20% increase in the basic value of the rate is determined.

Table VIII below shows the ratio of activity between theophylline and Product for these two parameters ED Theo/ED Product.

ED Theo inotropic function $= 8 \times 10^{-4}M$

chronotropic function $= 4 \times 10^{-4}M$

Table VIII - Cardiac activity

Product	Inotropic function	Chronotropic function
6	5	6
8	10	2
9	50	25
10	4	15
17	<1	<1

5. Motor activity

The measurement of the neurosedative effect is based on the test of activity measurements in mice. Male mice weighing on average 25 to 30 g receive 55 and 166 µmol/kg of the test products intraperitoneally, and the control animals receive the corresponding doses of the vehicle. Five minutes after the administration, the animals are placed in activity-measuring cages, which record their movements digitally by means of the interruption of beams of light. The results are recorded in Table IX and expressed as the percentage variation (increase ↑ or decrease ↓) in activity compared with the controls during a period of 50 minutes following the administration.

Table IX - spontaneous activity - % variation compared with the controls.

PRODUCT	55 µmol/kg	166 µmol/kg
6	↘ 25	↘ 57
8	↘ 53	↘ 83
9	↘ 74	↘ 83
10	↘ 13	↘ 73
17	↗ 28	↘ 17
23	↘ 43	↘ 56
Theophylline	↗ 130	↗ 170

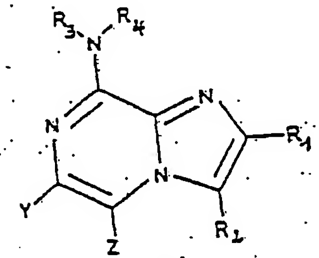
Naturally, the results of the trials presented above have been given only by way of illustration of the pharmacological properties which may be possessed by the compounds of the invention. The latter may hence be combined with any suitable excipient customarily used in human or veterinary therapy for the purpose of preparing and presenting pharmaceutical compositions which may be administered in the field of application of antispasmodics, uterine relaxants, bronchodilators, cardiac analeptics and neuro-sedatives. Thus, these compositions may take conventional pharmaceutical or modified-release forms, intended for oral or parenteral administration or administration via the mucosal and cutaneous linings, and containing the desired dose of active agent.

Naturally, the dosage and the methods of administration will, for each case, be left to the judgment and decision of the treating practitioner.

It is self-evident that the present invention has been described only in purely explanatory fashion and without any implied limitation, and that any expedient modification may be applied thereto without departing from the scope thereof.

CLAIMS

1. 8-Amino- and 8-alkylaminoimidazo[1,2-a]pyrazine compounds, as well as their derivatives corresponding to the formula (I) below and their salts that are compatible with pharmaceutical application, which correspond to the formula:



(I)

in which formula:

- Y and Z independently denote:
  - a) a hydrogen atom,
  - b) a halogen atom such as F, Cl, Br or I,
  - c) CO_2H,
  - d) CN,
  - e) a linear or branched C_1-C_5 alkyl radical,
  - f) a C_1-C_5 alkoxy radical,
  - g) CF_3
  - h) $-N\begin{smallmatrix}\diagup R_3\\ \diagdown R_4\end{smallmatrix}$, with R_3 and R_4 as defined below;

- R_1 and R_2, when they are independent, denote,
  - a) a hydrogen atom,
  - b) a halogen atom such as F, Cl, Br or I,
  - c) a linear or branched C_1-C_5 alkyl radical,
  - d) a radical $-(CH_2)_n-CO_2R_5$, with R_5 denoting a C_1-C_5 alkyl radical and n being between 0 and 4,
  - e) a phenyl radical, optionally substituted,
  - f) $CO-N\begin{smallmatrix}\diagup R_6\\ \diagdown R_7\end{smallmatrix}$,

with R_6 and R_7 independently denoting a hydrogen atom, a linear or branched C_1-C_5 alkyl radical or an aryl radical,

g) CN,

h) $CH_2-N\begin{matrix} R_6 \\ R_7 \end{matrix}$,

i) NH_2,

j) CH_2Cl,

k) CH_2OH,

l) CF_3,

m) $SO_2-N\begin{matrix} R_6 \\ R_7 \end{matrix}$,

n) $-NO_2$,

o) $-NO$,

p) a C_3-C_6 cycloalkyl radical,

q) an acyl radical,

r) a linear or branched C_1-C_5 alkylthio radical;

. R_1 and R_2, when they are linked to one another, denote $-CH_2-CH_2-CH_2-CH_2-$,

. R_3 and R_4 independently denote:

a) a hydrogen atom

b) a linear or branched C_1-C_5 alkyl radical, capable of bearing one or more hydrogen atoms or a hydroxy, $N(C_1-C_4\ alkyl)_2$, carbamoyl or C_1-C_4 alkoxy radical, either a C_3-C_6 cycloalkyl radical or a phenyl radical,

c) a C_1-C_5 acyl radical,

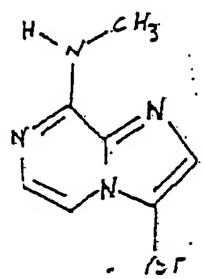
d) a furfuryl radical,

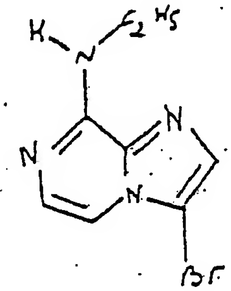
. R_3 and R_4, linked to one another denote $-CH_2-CH_2-CH_2-CH_2-CH_2$ or $-CH_2-CH_2-X-CH_2-CH_2-$ in which X denotes O or S.

2. The compounds as claimed in claim 1, which correspond to the formula (I) in which R_3 = H, R_4 = H or a methyl or ethyl radical, R_1 = H or an ethyl carboxylate group, Y and Z denote either H or Br and R_2 denotes Br or H.

3. The compounds as claimed in claim 1 or 2, which correspond to the formula (I) in which R_3 = H, R_4 = CH_3 or C_2H_5, Y = H, Z = H, R_2 = Br and R_1 = H, namely, respectively the compounds of formulae:

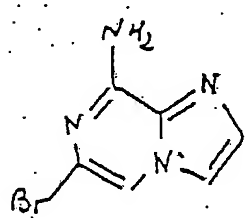
C_2H_5, Y = H, Z = H, R_2 = Br and R_1 = H, namely, respectively the compounds of formulae:





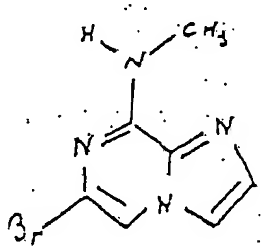
having, respectively, a melting point of 143°C and 82°C.

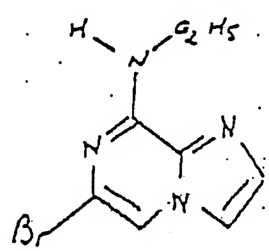
4. A compound as claimed in claim 1 or 2, which corresponds to the formula (I) in which Y denotes a bromine atom and R_1, R_2, R_3, R_4 and Z denote hydrogen atoms, namely the compound of formula



having a melting point of 210°C.

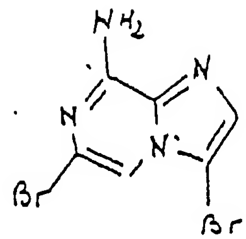
5. The compounds as claimed in claim 1 or 2, which correspond to the formula (I) in which R_3 = H, R_4 = CH_3 or C_2H_5, Y = Br, Z = H, R_2 = H, and R_1 = H, namely, respectively, the compounds of formulae:





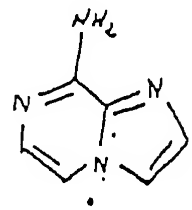
having, respectively, a melting point of 162°C and 99°C.

6. A compound as claimed in claim 1 or 2, which corresponds to the formula (I) in which R_3 = H, R_4 = H, Y = Br, Z = H, R_2 = Br and R_1 = H, namely the compound of formula:



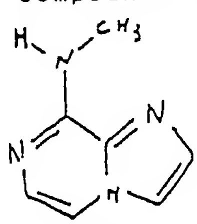
having a melting point of 246°C.

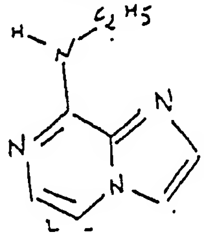
7. A compound as claimed in claim 1 or 2, which corresponds to the formula (I) in which Y, Z, R_1, R_2, R_3 and R_4 denote hydrogen atoms, namely the compound of formula:



having a melting point of 220°C.

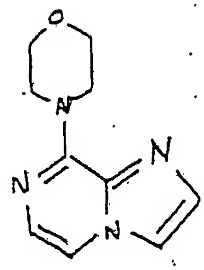
8. The compounds as claimed in claim 1 or 2, which correspond to the formula (I) in which Y, Z, R_1, R_2 and R_3 denote hydrogen atoms and R_4 denotes a methyl or ethyl radical, namely, the compounds of formulae:





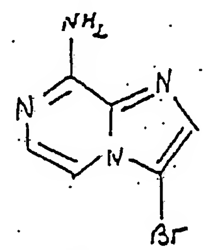
having, respectively, a melting point of 96°C and 98°C.

9. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y, Z, R_1 and R_2 denote hydrogen atoms and R_3 and R_4 are linked to one another to denote a $-(CH_2)_2-O-(CH_2)_2-$ radical, namely the compound of formula:



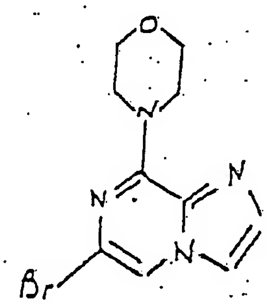
having a melting point of 127°C.

10. A compound as claimed in claim 1 or 2, which corresponds to the formula (I) in which Y, Z, R_1, R_3 and R_4 denote hydrogen atoms and R_2 denotes a bromine atom, namely the compound of formula:



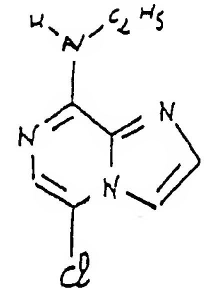
having a melting point of 239°C.

11. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y denotes a bromine atom, Z, R_1 and R_2 denote hydrogen atoms and R_3 and R_4 are linked to one another to denote a $-(CH_2)_2-O-(CH_2)_2-$ radical, namely the compound of formula:



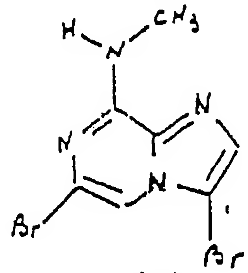
having a melting point of 191°C.

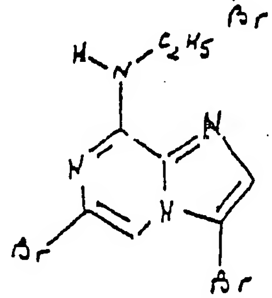
12. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y, R_1, R_2 and R_3 denote hydrogen atoms, Z denotes a chlorine atom and R_4 denotes a C_2H_5 radical, namely the compound of formula:



having a melting point of 94°C.

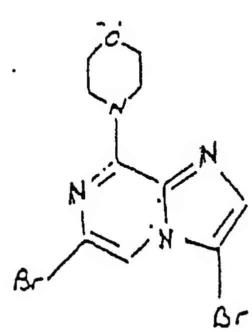
13. The compounds as claimed in claim 1 or 2, which correspond to the formula (I) in which Y and R_2 denote bromine atoms, Z, R_1 and R_3 denote hydrogen atoms and R_4 denotes a methyl or ethyl radical, namely the compounds of formulae:





having, respectively, a melting point of 229°C and 131°C.

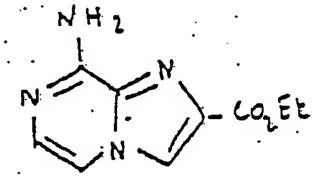
14. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y and R_2 denote bromine atoms, Z and R_1 denote hydrogen atoms and R_3 and R_4 are linked to one another to denote a $-(CH_2)_2-O-(CH_2)_2-$ radical, namely the compound of formula:

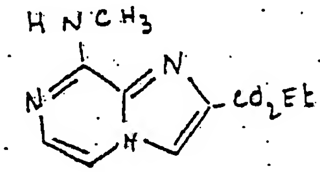


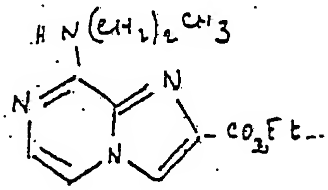
having a melting point of 151°C.

15. The compounds as claimed in Claim 1 or 2, which correspond to the formula (I) in which Y, Z, R_2 and R_3

denote hydrogen atoms and R_4 hydrogen or a $-CH_3$ radical or a $-C_3H_7$ radical, and R_1 denotes a $-CO_2C_2H_5$ group, namely t compounds, respectively of formulae:

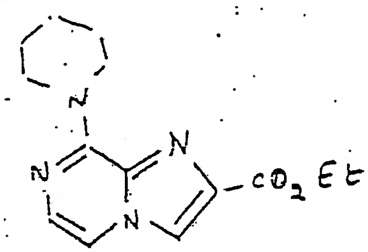


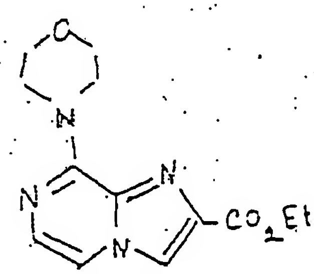




having, respectively, a melting point of 230°C, 184°C and 145°C.

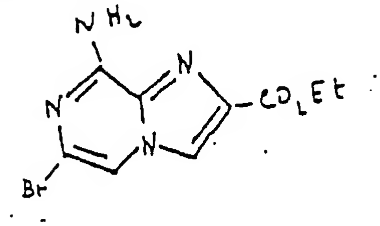
16. The compounds as claimed in claim 1, which correspond to the formula (I) in which Y, Z and R_2 denote hydrogen atoms, R_1 denotes a $-CO_2C_2H_5$ and R_3 and R_4 are linked to one another to denote either a $-(CH_2)_5-$ radical or a $-(CH_2)_2-O-(CH_2)_2-$ radical, namely the compounds, respectively, of formulae:

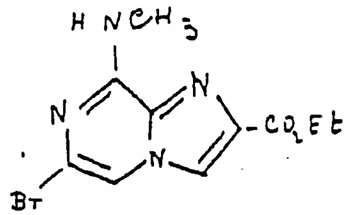


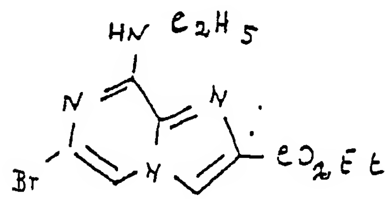


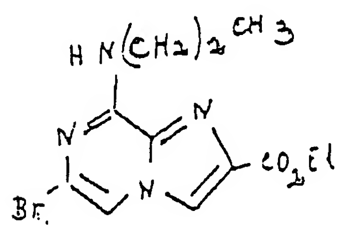
having, respectively, a melting point of 114°C and 155°C.

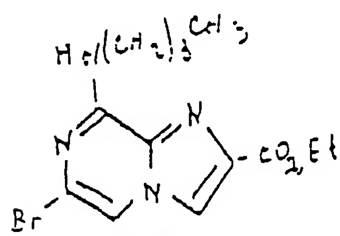
17. The compounds as claimed in claim 1, which correspond to the formula (I), in which Y denotes a bromine atom, Z, R_3 and R_2 denote hydrogen atoms, R_1 denotes a $-CO_2C_2H_5$ and R_4 denotes either a hydrogen atom or one of the radicals $-CH_3$, $-C_2H_5$, $-C_3H_7$, n-C_4H_9, s-C_4H_9, namely the compounds, respectively, of formulae:

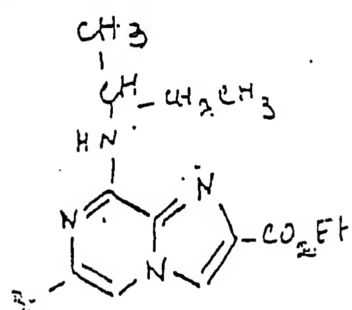






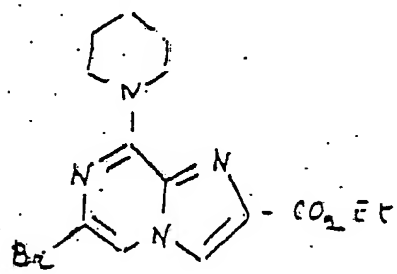


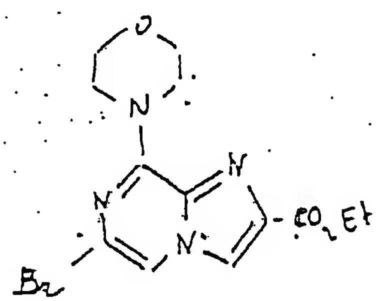




having, respectively, a melting point of 245°C, 234°C, 180°C, 190°C, 176°C and 187°C.

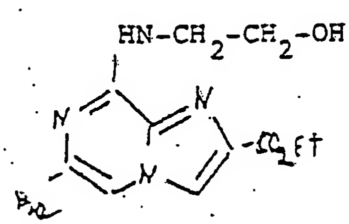
18. The compounds as claimed in claim 1, which correspond to the formula (I) in which Y denotes a bromine atom, Z and R_2 denote hydrogen atoms, R_1 denotes a $-CO_2C_2H_5$ group and R_3 and R_4 are linked to one another to denote either a $-(CH_2)_5-$ radical, or a $-(CH_2)_2-O-(CH_2)_2-$ radical, namely the compounds, respectively, of formulae:





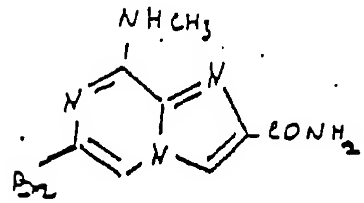
having, respectively, a melting point of 134°C and 140°C.

19. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y denotes a bromine atom, Z, R_2 and R_3 denote hydrogen atoms, R_4 denotes a $-(CH_2)_2OH$ radical and R_1 denotes a $-CO_2C_2H_5$ group, namely the compound of formula:



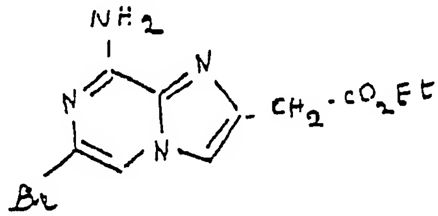
having a melting point of 208°C.

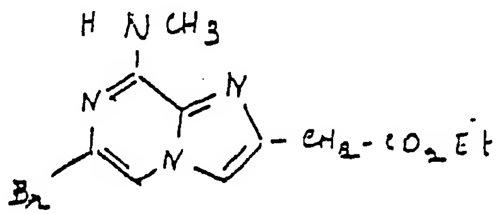
20. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y denotes a bromine atom, Z, R_2 and R_3 denote hydrogen atoms, R_4 denotes a $-CH_3$ radical and R_1 denotes a $-CONH_2$ group, namely the compound of formula:



having a melting point of 312°C.

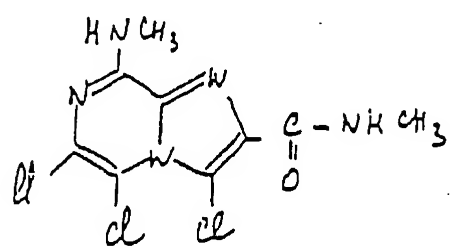
21. The compounds as claimed in claim 1, which correspond to the formula (I) in which Y denotes a bromine atom, Z, R_2 and R_3 denote hydrogen atoms, R_1 denotes a $-CH_2CO_2C_2H_5$ and R_4 denotes either hydrogen or a methyl radical, namely the compounds, respectively, of formulae:





having, respectively, a melting point of 181°C and 104°C.

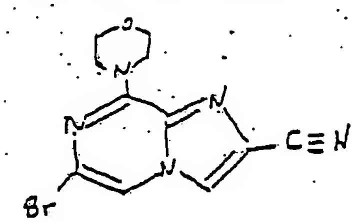
22. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y, Z and R_2 denote chlorine atoms, R_3 denotes hydrogen, R_4 denotes a $-CH_3$ radical and R_1 denotes a $CONHCH_3$ group, namely the compound of formula:



having a melting point of 262°C.

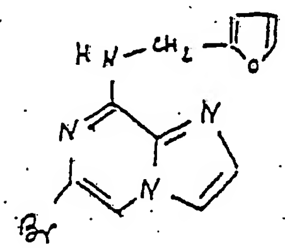
23. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y denotes a bromine atom, Z and R_2 denote hydrogen atoms, R_1 denotes a -CN radical and R_3 and R_4 are linked to one another to denote a $-(CH_2)_2-O-$

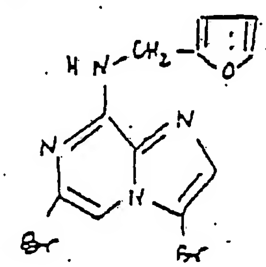
$(CH_2)_2$- radical, namely the compound of formula:



having a melting point of 265°C.

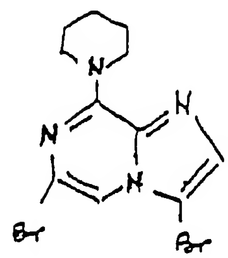
24. The compounds as claimed in claim 1, which correspond to the formula (I) in which Y denotes a bromine atom, Z, R_1 and R_3 denote hydrogen atoms, R_2 denotes either a hydrogen atom or a bromine atom and R_4 denotes a $-CH_2$-(furyl) group, namely the compounds, respectively, of formulae:





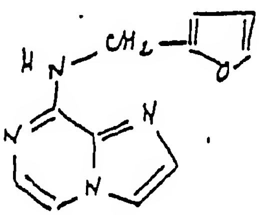
having, respectively, a melting point of 164°C and 143°C.

25. A compound as claimed in claim 1, which corresponds to the formula (I) in which Y and R_2 denote bromine atoms, Z and R_1 denote hydrogen atoms and R_3 and R_4 are linked to one another to denote a $-(CH_2)_5$, namely the compound of formula:



having a melting point of 72°C.

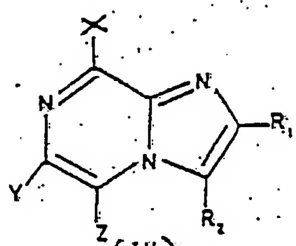
26. A compound as claimed in claim 1, in which Y, Z, R_1, R_2 and R_3 denote hydrogen atoms and R_4 denotes a $-CH_2$  group, namely the compound of formula:

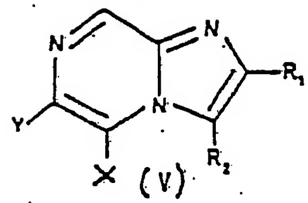


This compound is pasty.

27. The compounds as claimed in any one of claims 1 to 26, which are the salts thereof resulting from the neutralization of the basic compounds corresponding to the formula (I) with an acid chosen from inorganic acids of the halogen hydracid type (such as hydrochloric acid, hydrobromic acid and hydriodic acid), phosphoric acid, sulfuric acid and the like, and chosen from organic acids of the carboxylic acid type, such as acetic acid, maleic acid, succinic acid, citric acid, tartaric acid, oxalic acid, malic acid, pivalic acid, heptanoic acid, lauric acid, salicylic acid, benzoic acid, glutamic acid, lactic acid and the like as well as from non-carboxylic acids such as isethionic acid and methanesulfonic acid, and more especially the salts of halogen hydracids such as the hydrochlorides, the salts of maleic acid, in particular the acid maleates, and the salts of methanesulfonic acid.

28. A process for preparing compounds as claimed in any one of claims 1 to 27, wherein the halogenated derivatives represented by the general formulae (IV) and (V)


(IV)


(V)

in which X is a halogen such as chlorine or bromine, the other radicals R_1, R_2, Y and Z having the meanings given in these claims, are converted to amines.

29. The compounds as claimed in any one of claims 1 to 27, as medicinal products used in human and veterinary therapy in the field of application of antispasmodics, uterine relaxants, bronchodilators, cardiac analeptics and neurosedatives.

30. A pharmaceutical composition, which contains at least one compound as claimed in any one of claims 1 to 27 in combination or otherwise with any excipient, the said composition having an application in human or veterinary therapy in the field of application of antispasmodics, uterine relaxants, bronchodilators, cardiac analeptics and neurosedatives.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 87/00756

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 487/04; A 61 K 31/495; // (C 07 D 487/04, 241:00, 235:00)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 487/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	EP, A, 0166609 (WELLCOME) 2 January 1986 see claims 1,7 --	1,30
X	EP, A, 0013914 (MERCK) 6 August 1980 see claim 1; page 2, lines 2-6 cited in the application --------	1,30

* Special categories of cited documents: [10]
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24th March 1988	- 3 MAY 1988
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	P.C.G. VAN DER PUTTEN

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 8700756
SA 20129

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 21/04/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0166609	02-01-86	AU-A- 4421485	02-01-86
		JP-A- 61024594	03-02-86
EP-A- 0013914	06-08-80	JP-A- 55100389	31-07-80
		US-A- 4242344	30-12-80
		AT-T- 2004	15-12-82

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82